



IL-21/IL-21R in Autoimmune Diseases

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Received date: January 29, 2015; Accepted date: April 20, 2016; Published date: April 29, 2016

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Abstract

Interleukin-21 (IL-21), the member of the γ -chain-related cytokine family, and its receptor (IL-21R), has been evidenced involving in the immune response, resulting in the development of autoimmune diseases, infectious diseases and tumors. This short communication reviews an overall outline of its genetic variants and expression in autoimmune diseases. It focuses on a series of recent studies that have supporting the pathogenic role through human or animal experiments *in vitro* or *in vivo*.

Keywords: IL-21; IL-21R; Autoimmune diseases

Introduction

Interleukin-21 (IL-21), found by Parrish-Novak J first in 2000, a novel cytokine produced by activated CD4⁺T cells or NKT cells, is a new member of the type I four- α -helical-bundle cytokine family, and closely homologizes with IL-2 and IL-15 in structure [1]. Its receptor, IL-21R, a class I cytokine receptor, shares the common γ chain with IL-2, IL-4 and IL-15, is expressed in lymphoid tissues including thymus, spleen and lymph nodes, as well as peripheral blood leukocytes [2]. It has been proved that IL-21/IL-21R pathway involves in autoimmune diseases by contributing to innate and acquired immune responses [3,4]. Moreover, recombinant IL-21 (rIL-21) showed antitumor activity in some tumor patients with metastatic melanoma (MM) and renal cell carcinoma (RCC) [5]. Thus here we review the present knowledge on the expression and role of IL-21/IL-21R in autoimmune diseases and provide some foundation for the intractable autoimmune diseases.

Genetic Variants in Autoimmune Diseases

With progress of biochemistry methods, genetics researches have demonstrated that the Single Nucleotide Polymorphisms (SNPs) of IL-21 or IL-21R genes are associated with the development of autoimmune diseases. In our previous Cross-Sectional study, we found a significant association between rs2221903 of IL-21 gene and Hashimoto thyroiditis (HT), and the IL-21R genotype frequencies of rs3093301 and rs2285452 were significantly different in HT patients compared with controls. And the haplotype AA containing the major alleles of rs4833837 and rs2221903 was associated with increased susceptibility to HT with an OR of 1.69 [6]. rs907715 SNP of IL-21 is significantly associated with Graves' disease (GD) as well, while the rs13143866 A allele is significantly associated with Graves' ophthalmopathy (GO) [7,8]. These findings indicated that individuals with the SNPs of the common IL-21 and/or IL-21R may have higher risk of autoimmune thyroid disease (AITD), containing HT, GD, GO and so on. In inflammatory bowel disease (IBD), Festen et al. found that four SNPs, including rs13151961, rs13119723, rs6840978 and

rs6822844, in the IL-2/IL-21 locus were strongly associated with ulcerative colitis (UC) and reached genome-wide significance in the pooled analysis, and a moderate association with Crohn's disease (CD) was also sought [9]. In systemic lupus erythematosus (SLE), Sawalha et al. also found a genetic association with two SNPs located within the IL-21 gene (rs907715 and rs2221903) and SLE. Furthermore, genotypes homozygous for the risk alleles were more frequent than the non-risk alleles ((rs907715 (GG versus AA), rs2221903 (GG versus AA)) [10]. These SNPs and genotype frequencies suggest that IL-21 and IL-21R polymorphisms are candidates association with autoimmune diseases in genetics.

Expression of IL-21/IL-21R in Autoimmune Diseases

In line with the genetic alterations, a large body of evidence indicated that the expression IL-21/IL-21R was up-regulated in autoimmune diseases.

For instance, the serum IL-21 levels in the GD patients were significantly higher than those in the control group with enzyme-linked immunosorbent assay (ELISA) [11,12], and increased percentages of IL-21⁺CD3⁺CD8⁻T cells or circulating IL-21-Tfh cells, were detected in GD and HT patients using flow cytometry (FCM). Additionally, follow-up analysis indicated that serum IL-21 and the percentage of circulating IL-21-Tfh cells decreased in some GD patients after treatment [11,13]. In SLE patients, significantly increased percentages of IL-21 expressing CD4⁺T-cells and CD8⁺T-cells were also found compared to healthy control [14]. All above confirmed that IL-21 is expressed in not only CD4⁺Tcells but also CD8⁺T-cells, and it is associated with the GD activity. For IBD, enhanced IL-21 RNA and protein expression of duodenal samples from untreated CD patients was seen by real time polymerase chain reaction (RT-PCR) and Western blotting [15]. IL-21mRNA of rectal mucosa from patients with active UC was also increased with RT-PCR compared to remittent UC patients and the healthy control group, and IL-21 gene expression was correlated with histological activity [16]. The high expression of IL-21 and the correlation with activity suggest a pivotal role of IL-21 in the pathogenesis of autoimmune diseases.

Besides the augmentation of IL-21, high-level expression of IL-21R has been found by damaged tissues. With situ hybridization and Western blotting up-regulation of IL-21R in samples of epidermis from systemic sclerosis (SSc) patients was detected [17]. In rheumatoid arthritis (RA), IL-21R was found in synovial biopsy samples using RT-PCR and in situ hybridization, it was also detected in both synovial macrophages and fibroblasts with double labeling, Western blotting with anti-IL-21R antibodies confirmed the expression of IL-21R protein in RA synovial fibroblasts [18]. In AITD, IL-21R mRNA in thyroid tissues of HT patients were observed with RT-PCR, immunohistochemical staining confirmed the expression of IL-21R protein in HT thyroid cells and lymphocytes [12]. IL-21R was also found up-regulated in draining lymph node (DLN) and spleen cells of EAU mice by RT-PCR and FCM [19]. So, the augmentation of IL-21, combining with high-level IL-21R, worsen the diseases.

Pathogenic Role of IL-21/IL-21R in Autoimmune Diseases

Studies conducted *in vivo* or *ex vivo* to explore the mechanism of IL-21/IL-21R pathway to support the view that it plays a decisive role in the pathogenesis of immune-mediated diseases.

Stimulating the isolated peripheral blood and synovial fluid T cells from RA patients with IL-21 and anti-CD3 antibody, higher level of tumor necrosis factor- α (TNF- α) and **interferon- γ** (IFN- γ) were detected in the supernatant, and blockade of the IL-21/IL-21R pathway with IL-21R.Fc can ameliorate both the clinical and histologic signs of collagen-induced arthritis [20,21]. In coeliac disease (CD), the expression of Stat4 and T-bet, two **Th1**-driving transcription factors, were reduced with neutralization of IL-21 in cultures of the lamina propria lymphocytes, and the production of **IFN- γ** was also inhibited. Administration of IL-21R/Fc to DSS-treated colitis mice attenuates inflammation and prevents mortality [15]. Thus, we speculated that IL-21 enhances the ongoing Th1 cell response in autoimmune disease.

In the lupus-prone MRL-Fas *lpr* mouse model, reduced proteinuria, fewer IgG glomerular deposits, reduced levels of circulating dsDNA Ab and total sera IgG1 and IgG2a, were observed in the mice treated with IL-21R.Fc fusion protein, as well resulted in an altered splenic B lymphocyte and reduced number of splenic T lymphocytes *ex vivo* function, suggesting that IL-21 impacts B cell function and regulates the production of autoantibodies leading to the autoimmune diseases [22].

Similarly, *in vitro*, cells in EAU patients cultured with IL-21 combined with TGF- β induced increased production of IL-17 [21], and also significantly increased IL-17 by PBMCs and CD4⁺T cells from Vogt-Koyanagi-Harada (VKH) patients [23]. Additionally, PBMCs from GD patients stimulated by IL-21 resulted in enhanced IL-17A [12]. These data suggest that IL-21 is critically involved in the regulation of Th17 cell differentiation.

All these observations reinforce the concept that IL-21/IL-21R could affect the autoimmune reaction by activating T cells, regulating B cells homeostasis in autoimmune diseases.

Conclusion

On account of the expression and pathogenic role of the IL-21 pathway, maybe it's a promising therapeutic approach for autoimmune diseases by targeting IL-21/IL-21R in the future, but investigations are needed to carry out to probe the further program.

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